REMARKS / ARGUMENTS

I. Petition / Restriction

Applicants did not have the opportunity to reply to the Decision on Petition because the Examiner did not advise Applicants of the Decision in time. Applicants' traversal is of record in the response filed on February 27, 2006. For at least these reasons the claims have unity of invention under the PCT rules.

II. Amendments and Status of Claims

Claims 9 and 13 are amended to state that the second polypeptide and the additional polypeptide are heterologous to the first polypeptide. Claims 36-38 are amended to be drawn to the invention under examination. These amendments do not introduce new matter.

Applicants acknowledge that claim 2 was amended in the response filed on February 27, 2006 and apologize for the error in identifying the claim status.

Claims 1, 2, 4-17, 20-38 and 79-83 are pending. Claims 20-24, 26-35 are withdrawn. Claims 1, 2, 4-17, 25, 36-38 and 79-83 are under prosecution.

Attached are:

- Howard RF, Jacobson KC, Rickel E, Thurman. Analysis of inhibitory epitopes in the Plasmodium falciparum rhoptry protein RAP-1 including identification of a second inhibitory epitope. J. Infect Immun. 1998 Jan; 66(1):380-6. [Abstract]
- AbD Serotec Excerpt from technical brochure from www.ab-direct.com.
- Ayyildiz. Technical Approach to Generate Polyclonal Antibodies Against Bacterially Expressed GST-PYK-C. Tr. J. Medical Sciences. 29 (1999) 355-360. [Abstract]
- Cassill JA, Whitney M, Joazeiro CA, Becker A, Zuker CS. Isolation of Drosophila genes encoding G protein-coupled receptor kinases. Proc Natl Acad Sci U S A. 1991 Dec 15;88(24):11067-70. [Pages 11067 & 11068]
- Lutzelschwab R, Klambt C, Rossa R, Schmidt O. A protein product of the Drosophila recessive tumor gene, l (2) giant gl, potentially has cell adhesion properties. EMBO J. 1987 Jun;6(6):1791-1797. [Pages 1791 & 1792]

- Schoneck R, Plumas-Marty B, Taibi A, Billaut-Mulot O, Loyens M, Gras-Masse H, Capron A, Ouaissi A. Trypanosoma cruzi cDNA encodes a tandemly repeated domain structure characteristic of small stress proteins and glutathione S-transferases. Biol Cell. 1994;80(1):1-10. [Pages 1 & 2]
- Philippe B, Brion JP, Coppens E, Octave JN. Generation of a monoclonal antibody to the carboxy-terminal domain of tau by immunization with the amino-terminal domain of the amyloid precursor protein. J Neurosci Res. 1996 Dec 15;46(6):709-19. [Abstract]
- Yu H, Nakano Y, Yamashita Y, Oho T and Koga T. Effects of antibodies against cell surface protein antigen PAc- glucosyltransferase fusion proteins on glucan synthesis and cell adhesion of Streptococcus mutans. Infect. Immun., 06 1997, 2292-2298, Vol 65, No. 6 [Abstract]
- Zhou FC, Xu Y, Bledsoe S, Lin R, Kelley MR. Serotonin transporter antibodies: production, characterization, and localization in the brain. Brain Res Mol Brain Res. 1996 Dec 31;43(1-2):267-78. [Abstract]

III. Indefiniteness 35 U.S.C. § 112, 2nd paragraph

The Examiner alleges that "second polypeptide" in claims 9-11 and "additional polypeptide" in claim 13 render the claims vague and indefinite. For the sole purpose of advancing the prosecution of this application, the claims are amended to recite that the second polypeptide and the additional polypeptide are heterologous to the first polypeptide.

Withdrawal of the objections under 35 U.S.C. § 112, second paragraph, is respectfully requested.

IV. 35 U.S.C. § 112, 1st paragraph (written description)

The Examiner rejects claims 1, 2, 4-17, 25, 36-38 and 79-83 under 35 U.S.C. §112, 1st paragraph, for alleged insufficient written description. Applicants traverse.

The Examiner repeats the same grounds for rejection without addressing Applicants' arguments. Applicants' traversal is based on a number of decisions by the Board of Patent Appeals and Interferences (BPAI) on claims that recite sequence variants or fragments. The BPAI's decisions provide clear guidance on applying the courts' decisions to claims that recite sequence variants or

fragments. Applicants showed how each decision is pertinent to the present application, that the Examiner's rejections are contrary to the BPAI, and that the rejections are therefore incorrect. The Examiner did not address any of these arguments.

Applicants remind the Examiner of Section 2163.04 of the MPEP which places the burden on the Examiner with regard to the written description requirement:

> "A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.
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> [...]
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> In rejecting a claim, the examiner must set forth express findings of fact which support the lack of written description conclusion [...]. These findings should [...] [e]stablish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. A general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description."

In *Ex parte Sun*, Appeal No. 2003-1993, Application No. 09/470,526 (Jan 20, 2004), the Board concluded that the specification had sufficient written description support. The facts presented in *Ex parte Sun* are analogous to the present application. The Examiner has not indicated why a skilled person would be unable to recognize that the inventors have invented the variants sharing structural features with the specific structure SEQ ID NO:14.

In *Ex parte Meyers*, Appeal No. 2003-1820, Application No. 09/464,039 (Aug. 31, 2004), the Board concluded that the specification had sufficient written description support. The facts presented in *Ex parte Meyers* are analogous to the present application. The Examiner has not indicated why this analysis (screening for variants that retain immunogenicity and computer-assisted methods to identify probable surface-exposed antigenic regions) cannot be used to assign functional immunogenicity to a polypeptide. The Examiner has not presented evidence to demonstrate that one of skill would doubt the credibility of applicant's assertion of immunogenic function.

In *Ex parte Bandman*, Appeal No. 2004-2319, Application No. 09/915,694 (Jan. 6, 2005), the Board concluded that the specification had sufficient written description support. The facts presented in *Ex parte Bandman* are analogous to the present application. The Examiner has not adequately explained and/or provided evidence to support the contention that the specification provides no disclosure of any particular structure to function/activity relationship.

In *Ex parte Chung*, Appeal No. 2004-2201, Application No. 09/788,476 (Nov. 22, 2004), the Board concluded that the specification had sufficient written description support. The facts presented in *Ex parte Chung* are analogous to the present application. The Examiner has not provided an analysis of why the function limitation ("immunogenic fragment" and "without loss of immunogenicity") is not an adequate identifier of the claimed genus of sequences. The Examiner has not stated why the variants cannot be characterized by their immunogenic function. The Examiner therefore has not met the initial burden of establishing insufficient written description.

In *Ex parte McElroy,* Appeal No. 2003-0936, Application No. 09/352,806 (Aug. 29, 2003), the Board concluded that the specification had sufficient written description support. The facts presented in *Ex parte McElroy* are analogous to the present application. The present claims recite a sequence which is a subsequence of a specifically disclosed whole. As is the case in *Ex parte McElroy*, the specification describes SEQ ID NOs:1 and 14 by naming their specific sequences and in so doing, there is *prima facie* description of each and every fragment within the whole sequence.

In *Ex parte Friedberg*, Appeal No. 2004-2314, Application No. 09/971,101 (Nov. 17, 2004), the Board concluded that the specification had sufficient written description support. The facts presented in *Ex parte Friedberg* are analogous to the present application. The present claims recite immunogenic fragments which are subsequences of a specifically disclosed polypeptide sequence. The specification provides the complete structure of the fragments since they are merely subsequences of the whole. The structural features that are common to the polypeptides of the claimed genus are the at least 12 contiguous amino acids. The Examiner has not adequately explained why this degree of structural similarity is inadequate to "constitute a substantial portion of the genus," as required by *Lilly*.

The facts of each Decision from the BPAI are analogous to the present application. The BPAI's decision in each case demonstrate that, by analogy, the present claims have sufficient written description.

Withdrawal of the rejections under 35 U.S.C. § 112, first paragraph (written description), is respectfully requested.

V. 35 U.S.C. § 112, 1st paragraph (enablement)

The Examiner rejects claims 1, 2, 4-17, 25, 36-38 and 79-83 under 35 U.S.C. §112, 1st paragraph, for alleged lack of enablement over the claim scope. Applicants traverse.

The Examiner states that "an isolated nucleic acid molecule consisting of the nucleic acid sequence which encodes the immunogenic fragment consisting of 12/50 consecutive amino acids of SEQ ID NO:14 or an isolated nucleic acid consisting of 38/100 consecutive nucleic acids of SEQ ID NO:1 are enabled". The Examiner points to certain references as evidence of this [page 10 of Office Action]. The Examiner then alleges that fragments of at least 12/50 amino acids or sequences comprising such fragments are not enabled, pointing to Niman et al. PNAS USA 1983. 80:4949-4953, Current Protocols in Immunology 1997 unit 9.7.5, and Reece et al. J Immunol 1994. 172:241 as evidence of this. The Examiner also deems Dr. Murdin's declaration under 37 C.F.R. 1.132 as unpersuasive.

(1) The Examiner alleges that fragments of at least 12/50 amino acids are not enabled. By the Examiner's reasoning, no full length protein larger than 12/50 amino acids should be able to elicit an immunogenic response. This is not true. Full-length proteins are routinely used to generate an immune response, e.g. for antibody production. Please see the attached technical excerpt from AbD Serotec, a company that makes antibodies commercially. AbD states that expressed domains (100 to 300 amino acids), typically longer than peptides (10 to 25 amino acids), provide more epitopes for antibody generation and that fragments larger than 100 amino acids generally fold into a rigid structure and are more likely to have 3-D epitopes present in the parental protein. Applicants also provide a number of references published before the filing date as examples showing that fragments are routinely used to elicit an immunogenic response.

See Howard RF et al. J. Infect Immun. 1998 Jan; 66(1):380-6. [Abstract], and also the references listed below.

(2) The Examiner alleges that sequences comprising fragments of at least 12/50 amino acids, including fusion proteins, are not enabled. Sequences such as fusion proteins comprising fragments of at least 12/50 amino acids were routinely used at the time the application was filed to elicit an immunogenic response. Applicants provide as evidence a number of references published before the filing date as examples showing that fusions comprising protein fragments were routinely used to elicit an immunogenic response. See:

- Ayyildiz. Tr. J. Medical Sciences. 29 (1999) 355-360. [Abstract]
- Cassill JA et al. Proc Natl Acad Sci U S A. 1991 Dec 15;88(24):11067-70. [See the second full paragraph on the left column of page 11068]
- Lutzelschwab R et al. EMBO J. 1987 Jun;6(6):1791-1797. [See the Abstract and Figure 1 on page 1792]
- Schoneck R et al. Biol Cell. 1994;80(1):1-10. [See the first paragraph on the right column of page 2]
- Philippe B et al. J Neurosci Res. 1996 Dec 15;46(6):709-19. [Abstract]
- Yu H et al. Infect. Immun., 06 1997, 2292-2298, Vol 65, No. 6 [Abstract]
- Zhou FC et al. Brain Res Mol Brain Res. 1996 Dec 31;43(1-2):267-78. [Abstract]

(3) The Examiner alleges that sequences comprising at least 12 amino acids have no upper limit, read on unknown fragments broader than SEQ ID NO:14 and having no function. Applicants point out that "at least 12" amino acids does have an upper limit of 552 amino acids, which is the full length of SEQ ID NO:14. The claimed sequences do not read on unknown fragments because the claimed sequences are sub-sequences of the specifically disclosed SEQ ID NO:14 (see *Ex parte Friedberg*, Appeal No. 2004-2314, Application No. 09/971,101 (Nov. 17, 2004). "Comprising" is a term routinely used in patent claims to refer to inclusion of non-essential elements and does not indicate that the scope of the claim is unknown. The claimed sequences do have function because the fragments and variants are specified in the claims as "immunogenic".

(4) The Examiner cites Niman et al. PNAS USA 1983. 80:4949-4953 ['Niman'] as evidence that only peptides consisting of 5 or 10 amino acids can induce antibody response and recognize the full length protein. This is inaccurate. The purpose of Niman's study is to test the stochastic model of immune recognition. Niman

does not say that larger sequences cannot induce an antibody response. Niman merely indicates that small peptides can do so [see page 4952 at bottom left "These results suggest that sufficient structural information for high-frequency recognition of intact proteins is contained in peptides as small as 13 amino acid residues."]. Actually, Niman then goes on to describe another study where a 56-residue fragment of interferon was used successfully to generate monoclonal antibodies [see page 4952 top right, referring to Arnheiter et al. Nature 1981. 294:278-280].

(5) The Examiner cites Current Protocols in Immunology 1997 unit 9.7.5 as evidence that peptides longer than 6 residues should be avoided because of increased impurity. Applicants submit that the Examiner's concern is misplaced. Even if it were true that chemically synthesized sequences are less pure with increased sequence length, there is no reason why sequences longer than 6 residues should have to be made by chemical synthesis. Page 19 lines 8-33, apge 21 lines 7-25, page 22 lines 13-20, and page 23 line 5 to page 26 line 17 of the specification describe in detail the methods, other than chemical synthesis, known in the art to make protein fragments. The references above [Howard RF et al.; Ayyildiz; Cassill JA et al.; Lutzelschwab R et al.; Schoneck R et al.; Philippe B et al.; Yu H et al.; and Zhou FC et al.] are ample evidence that non-chemical synthesis were routinely used to make fragments.

(6) The Examiner cites Reece et al. J Immunol 1994. 172:241 ['Reece'] as evidence that sequences longer than a 31-mer are unsuitable or lack utility because "many epitopes would be missed if the peptides used were long". Applicants submit that the Examiner misunderstood the reference. The purpose of Reece's study is to assess "the sensitivity and efficiency of the pooling/decoding method for identifying T helper cell epitopes using PBMC and pools of synthetic peptides." [page 242, second paragraph at right]. In stating that "Many epitopes would be missed if either long (31mers) or short (less than 12mers) peptides were used", Reece was referring to the use of the peptides in a scanning epitope assay to identify where a T-helper cell epitope is located within a gene sequence. Reece was not talking about using peptides or fragments to generate an immune response. Larger fragments in fact make better antigens because they provide more epitopes for antibody generation and, for fragments larger than 100 amino acids, can generally fold into a rigid structure and are more likely to have 3-D epitopes present in the parental protein (see the enclosed AbD Serotec technical excerpt).

(7) The Examiner states that the inventor's Declaration under 37 C.F.R. 1.132 is not persuasive because it does not show evidence or support that DNA vaccines for Chlamydial infection are routine in the art and that, further, the claimed composition has not been shown to be protective against Chlamydia. Dr. Murdin is a person skilled in the art. His Declaration is evidence that the present application discloses at least one true candidate against Chlamydia, and that the references Allen et al. J. Immun. 1991. 147:674-679, Battereiger et al. 1996. Infect. Immun. 64:2839-2841, and Murdin et al. 2000. J. Infect. Diseases 181(Suppl. 3):S552-S557 do not accurately show the state of the art. Dr. Murdin's declaration has weight in this respect.

(8) Applicants remind the Examiner of Section 2164.04 of the MPEP which places the burden on the Examiner with regard to the enablement requirement: "[T]he examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." Applicants have cited a number of BPAI decisions by the BPAI which provide clear guidance on applying the courts' decisions to claims that recite sequence variants or fragments. Applicants showed how each decision is pertinent to the present application, that the Examiner's rejections are contrary to the BPAI, and that the rejections are therefore incorrect. The Examiner did not address this in the Office Action.

In *Ex parte Sun*, Appeal No. 2003-1993, Application No. 09/470,526 (Jan. 20, 2004), the Board concluded that the claims were enabled. The facts presented in *Ex parte Sun* are analogous to the present application. The Board concluded it is irrelevant whether an enabling disclosure is provided through broad terminology or illustrative examples. The Examiner has not advanced an acceptable reasoning as is required for meeting the burden of showing non-enablement.

In *Ex parte Meyers*, Appeal No. 2003-1820, Application No. 09/464,039 (Aug. 31, 2004), the Board concluded that the claims were enabled. The facts presented in *Ex parte Meyers* are analogous to the present application. The Examiner has not indicated why the disclosed methods of screening variants for immunogenicity, or the disclosed computer-assisted methods to identify probable surface-exposed antigenic regions, cannot be used to assign functional immunogenicity to a polypeptide, nor why they are not an art-accepted methods of determining immunogenic function.

In *Ex parte Bandman*, Appeal No. 2004-2319, Application No. 09/915,694 (Jan. 6, 2005), the Board concluded that the claims were enabled. The facts presented in *Ex parte Bandman* are analogous to the present application. The Examiner has not explained and/or provided evidence why a variant that is at least 95% identical to SEQ ID NO:14 would not retain immunogenicity. The Examiner bears the initial burden of showing nonenablement and has not met it.

In *Ex parte Chung*, Appeal No. 2004-2201, Application No. 09/788,476 (Nov. 22, 2004), the Board concluded that the claims were enabled. The Examiner has not provided an analysis of why the amount of work required to practice the invention throughout its scope would be considered undue instead of routine.

In *Ex parte McElroy,* Appeal No. 2003-0936, Application No. 09/352,806 (Aug. 29, 2003), the Board concluded that the claims were enabled. The facts presented in *Ex parte McElroy* are analogous to the present application. The Examiner has not indicated why the screening method and computer-assisted analysis cannot be used to assign functional immunogenicity to a polypeptide, nor why they are not an art-accepted methods of determining immunogenic function. Applicants submit that given these teachings, the amount of experimentation is reasonable.

In *Ex parte Friedberg*, Appeal No. 2004-2314, Application No. 09/971,101 (Nov. 17, 2004), the Board concluded that the claims were enabled. The facts presented in *Ex parte Friedberg* are analogous to the present application. As the Board pointed out, the enablement requirement is met if the description enables any mode of making and using the invention. The present specification enables use of the fragments for making antibodies and so the enablement requirements are met.

The facts of each Decision from the BPAI are analogous to the present application. The BPAI's decision in each case demonstrate that, by analogy, the present claims are enabled.

Withdrawal of the rejections under 35 U.S.C. § 112, first paragraph (enablement) is respectfully requested.

VI. Concluding Remarks

In view of the above amendments and remarks, reconsideration and favorable action on all pending claims are respectfully requested. If any questions or issues remain, the Examiner is invited to contact the undersigned at the telephone number set forth below so that a prompt disposition of this application can be achieved.

If a fee is required for an extension of time which is not accounted for, such an extension is requested and the U.S.P.T.O. is authorized to withdraw from our Deposit Account Number 19-0741 any fee required.

Respectfully submitted,

Date: Aug 23, 2006

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